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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,534	12/13/2001	Burton G. Christensen	P-011-RC2	7635

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EXAMINER	
SHIBUYA, MARK LANCE	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,534	CHRISTENSEN ET AL.	
	Examiner	Art Unit	
	Mark Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2002*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-35* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Objection to the Specification

1. A substitute specification excluding the claims is required pursuant to 37 CFR 1.125(a) because no specification appears in the file. It is noted that a Notice to file missing parts of the application, mailed 3/25/2002, required a substitute specification because the original had improper margins. It is further noted that in the Request for a corrected filing receipt, filed 5/22/2002, applicant requested the following:

> Under "Domestic Priority data as claimed by applicant, after "THIS APPLICATION IS A CON OF 09/493,462 FILED 01/28/2000", please add:
>
> "which is a continuation of U.S. application serial no. 09/327,904 filed 06/08/1999."

A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and (c)

Election/Restrictions

2. The applicant is invited to note please, that claims 29, 32 are listed as "Group VII, etc." and claim 34 is listed as "Group IX, etc." but in actuality contain within those claims a large number of separate and distinct inventions. If claims 2 and 32 or claim 34 are / elected, election of a *single invention* from within this group of claims is required as specifically set forth (see Group VII, etc., and Group IX, etc., below).

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 3-15, drawn to methods for identifying multimeric ligand compounds which bind cellular receptors and possess multibinding properties, comprising identifying a ligand or a mixture of ligands, identifying a *library of linkers*, preparing a multimeric ligand compound library, and assaying the multimeric ligand compounds, classifiable in class 435, subclass 7.1.

II. Claims 2-15 and 30, drawn to methods for identifying multimeric ligand compounds which bind cellular receptors and possess multibinding properties, comprising identifying a *library of ligands*, identifying a linker or mixture of linkers, preparing a multimeric ligand compound library, and assaying the multimeric ligand compounds, classifiable in class 435, subclass 7.1.

III. Claims 16 and 18-24, drawn to a library of multimeric ligand compounds which bind cellular receptors and possess multibinding properties, wherein the library is prepared by identifying a ligand or a mixture of ligands, identifying a *library of linkers*, and preparing a multimeric ligand compound library by combining the ligands with the library of linkers, classifiable in class 530, subclass 300.

IV. Claims 17-24, drawn to drawn to a library of multimeric ligand compounds which bind cellular receptors and possess multibinding properties, wherein the library is prepared by identifying a *library of ligands*, identifying a linker

or mixture of linkers, and preparing a multimeric ligand compound library by combining the ligands with the library of linkers, classifiable in class 530, subclass 300.

V. Claims 25-27, drawn to an iterative method for identifying multimeric ligand compounds which bind cellular receptors and possess multibinding properties, classifiable in class 435, subclass 7.1.

VI. Claims 28, 31, drawn to a multi-binding compound comprising 2 to 10 ligands which are covalently attached to a linker or linkers, said ligands comprising a ligand domain capable of binding to a cellular receptor; and pharmaceutical compositions thereof, classifiable in class 530, subclass 300.

VII, etc. Claims 29 and 32, drawn to a multi-binding compound represented by formula I: $(L)_p(X)_q$, wherein each L is independently selected from ligands comprising a ligand domain capable of binding to a receptor, X is a linker, p and q are integers; and pharmaceutical compositions thereof, classifiable in class 530, subclass 300.

It is noted that claims 29 and 32 contain a large number of independent and distinct inventions. If this group is selected, then election of a single invention wherein the following symbols of formula I are defined is required:

p and q must be specifically defined. For example, $(L)_2 (X)_2$.

Please see paragraph 2 above and the below explanations, of why Group VII, etc. contains a large number of independent and distinct inventions.

VIII. Claims 33 and 35, drawn to a method for treating a pathologic condition mediated by cellular receptors comprising administering a pharmaceutical composition comprising an effective amount of a multi-binding compound comprising 2 to 10 ligands which are covalently attached to a linker or linkers, said ligands comprising a ligand domain capable of binding to a cellular receptor, classifiable in class 514, subclass 2.

IX, etc. Claim 34, drawn to a method for treating a pathologic condition mediated by cellular receptors comprising administering a pharmaceutical composition represented by formula I: $(L)_p(X)_q$, wherein each L is independently selected from ligands comprising a ligand domain capable of binding to a receptor, X is a linker, p and q are integers, classifiable in class 514, subclass 2.

It is noted that claims 29 and 32 contain a large number of independent and distinct inventions. If this group is selected, then election of a single invention wherein the following symbols of formula I are defined is required:

p and q must be specifically defined. For example, $(L)_2 (X)_2$.

Please see paragraph 2 above and the below explanations, of why Group IX, etc. contains a large number of independent and distinct inventions.

Applicants should note that particular generic claims are listed in multiple groups. Upon election, the generic claims will be examined according to the elected groups

The inventions are distinct, each from the other because of the following reasons:

Inventions of Groups I, II, and V and the Inventions of Groups III, IV, VI, and VII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of Groups I, II, V, drawn to methods of identifying multimeric compounds which bind cellular receptors, have different effects from the inventions of Groups III, IV, VI and VII, drawn to multimeric compounds which bind cellular receptors and libraries of ligands or linkers.

Inventions of Groups I, II, V and the Inventions of Groups VIII and IX are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions because Groups I, II and V are methods for identifying multimeric compounds which bind cellular receptors, which is a different function from the methods of treatment of Groups VIII and IX.

Inventions of Groups I and II and the Invention of Group V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different

effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different modes of operation because the method of identifying multimeric ligand compounds of Group V is an iterative method, which is different from the non-iterative methods of Groups I and II.

Inventions of Groups III, IV, VI and VII and Inventions of Groups VIII and IX are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the multimeric compounds and libraries of ligands or linkers of Groups III, IV, VI and VII, may be used in methods of killing insects by insecticides, which are different from the methods of treatment of Groups VIII and IX.

Inventions of Groups I and III and the Inventions of Groups II and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of Groups I and III comprise libraries of linkers and methods thereof and so have different molecular structures from the Inventions of Groups II and IV, which comprise libraries of ligands and methods thereof.

Inventions of Group III and IV and the Invention of Groups VI and VII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions,

or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of Group III and IV are drawn to libraries of multimeric ligand compounds, and so have different molecular structures from the multi-binding compound of Groups VI and VII.

Inventions of Groups VI and VIII and the Inventions of Groups VII and IX are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the compounds and methods of treatment therewith, wherein the multi-binding compound comprises2 to 10 ligands covalently attached to a linker or linkers, of Groups VI and VIII have different molecular structures from the molecules of the compounds and methods of treatment, therewith, of Groups VII and IX, which have the formula $(L)_p(X)_q$, *e.g.*, Ligand-Ligand-Ligand-Linker-Linker-Linker, and so have different modes of operation.

The inventions of Group VII, etc., and Group IX, etc., wherein the compounds are specifically defined as to p and q of the formula $(L)_p(X)_q$, are test compounds with structurally distinct core structures and so are unrelated each to the other within their respective groups (*i.e.*, Group VII, etc., and Group IX, etc. Test compounds with structurally distinct core structures are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, test compounds with structurally distinct core structures are presumed to represent independent and distinct inventions, subject to a restriction requirement

pursuant to 35 U.S.C. 121 and 37 CFR 1.1141 et seq. The examination of more than one structurally distinct core structure would now pose an undue burden on the Office.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Election of Species

3. This application contains claims directed to the following patentably distinct species of the claimed invention: multimeric ligand compounds of 1) **ligands** and 2) **linkers**.

The specification at p. 10, states that **ligands** can be categorized as G-protein coupled receptors, tyrosine kinase linked receptors, guanylate-cyclase linked receptors, nuclear steroid receptors and adhesion molecules. The specification at pp. 11-22, 24, 25 and 27, provides Tables of examples of these classes of receptors. The specification at p. 65 states that examples of ligands useful for the invention are ligands for the muscarinic receptors; the alpha2, beta1 and beta2 adrenergic receptors, the 5-HT receptors, the $GABA_A$ receptor, the melatonin receptor; the angiotensin I receptor, the erythropoietin receptor; the dopamine 1 and 2 receptors; the A2 adenosine receptor, the nicotinic receptors and the steroid receptors.

The specification at p. 65 provides examples for **linkers** for the 5-HT receptor; at p. 68 for the nicotinic receptor; at p. 69 for the steroid receptors. The specification at

pp. 109-118 provides exemplary linkers identified as X-1 through X-418, and combinations thereof.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for a specific multimeric ligand compound of specific **ligand(s)** *and* specific **linker(s)** and prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. **Currently, 1, 2, 16, 17, 25, 28, 29, 31-35 are generic.**

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

4. Claims 9 and 18 are generic to a plurality of disclosed patentably distinct species comprising linker or linkers selected from the group flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization / polarizability and amphiphilic linkers. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

5. Claims 13 and 22 are generic to a plurality of disclosed patentably distinct species comprising ligand reactive functionality selected from the group of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record

showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

6. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark Shibuya
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